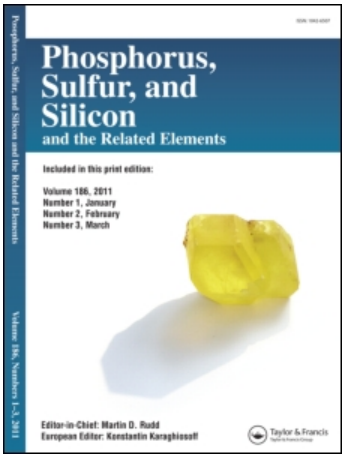

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Nucleoside Phosphoramidate Analogues with Modification in the Bridging Positions of the Phosphodiester Linkage

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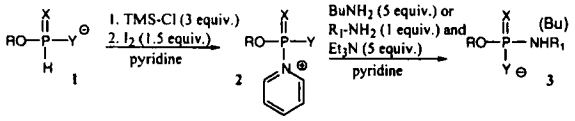
Phosphoramidate modified DNA oligomers[1] have recently been shown to have promising properties for antisense/antigene applications. An efficient method, for the preparation of nucleoside P3'→N5' and N3'→P5' phosphoramidates and their thio analogues **3** was developed[2]. It consists of the oxidative generation of a pyridine adduct of type **2** of nucleoside metaphosphate from the corresponding nucleoside H-phosphonate, nucleoside H-phosphonothioate or nucleoside H-phosphonoodithioate monoester, and its consecutive clean reaction with 5'- or 3'-aminonucleosides in the presence of triethylamine.



1-3a, X = Y = O, R = 5'-O-DMT-thymidin-3'-yl
1-3b, X = Y = O, R = 3'-O-DMT-thymidin-5'-yl
1-3c, X = O, Y = S, R = 5'-O-DMT-thymidin-3'-yl
1-3d, X = Y = S, R = 5'-O-DMT-thymidin-3'-yl

R_1 = 5'-O-*t*-BDMS-thymidin-3'-yl
or 3'-O-*t*-BDMS-thymidin-5'-yl

To enable efficient oxidation of the nucleoside H-phosphon(othio)ate monoesters to the corresponding metaphosphate intermediates, **1a-c** were converted to their trimethylsilyl diesters *via* treatment with TMS-Cl, prior to I_2 addition. In the instance of H-phosphonodithioate monoester **1d** the silylation with TMS-Cl improved the yields of the product, although no evidence for the formation of silyl ester for **1d** was apparent. In this approach, no phosphorus protecting group is necessary. Yields of isolated dimers range from 69 to 89%. This approach is also applicable for formation of phosphoramidates (and thioanalogues) from alkylamines (*e.g.* butylamine, yields ~70%).

References

[1] S. Gryaznov, *et. al., Nucleic Acids Res.*, **24,** 1508–1514 (1996).
[2] I. Kers, J. Stawinski, and A. Kraszewski, *Tetrahedron Lett.*, **39,** 1219–1222 (1998).